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10/559,647	07/31/2006	Rosanne M Crooke	ISPH-0595USA	5096

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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,647	CROOKE ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6,8-11,50 and 52-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,8-11,50 and 54-66* is/are rejected.

7)☒ Claim(s) *52 and 53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/11/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of group I in the reply filed on 4/11/07 is acknowledged.

Applicant's election with traverse of SEQ ID NO: 87 in the reply filed on 4/11/07 is acknowledged. The traversal is on the ground(s) that SEQ ID NO: 87 and SEQ ID NO: 88 share a common core because the 20-mers share 9 contiguous nucleobases. This is not found persuasive because although the sequences share 9 contiguous nucleobases, a search for one of the sequences will not necessarily return art against the other sequence. Since the sequences comprise nucleotides that are not identical, each of the sequences must be uniquely searched. As explained in the office action mailed on 12/11/06, a significant structure must be shared by each of the sequences, whereas each of the instantly claimed sequences is defined by a specific sequence of nucleotides.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 3, 6, 8-11, 50 and 52-66 are pending in the instant application. The subject matter of the claims that is not drawn to the elected invention (SEQ ID NO: 87) has been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/11/07.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application No. 60/475,402 and Application No. 10/684,440, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The applications do not teach antisense compounds that are targeted specifically to the range of nucleotides "12380-13493" of instant SEQ ID NO: 4 and do not teach the sequence of instant SEQ ID NO: 87.

Therefore, the instant claims are accorded an effective filing date of 6/2/04, the filing date of PCT/US04/14540.

Specification

The disclosure is objected to because of the following informalities: The specification discloses that GenBank accession number NM_005577.1 is incorporated herein as instant SEQ ID NO: 4 (see page 127 of the instant specification). However, upon a review of GenBank accession number NM_005577.1, GenBank accession number NM_005577.1 is 6489 nucleotides in length, wherein applicant is claiming antisense compounds targeted to nucleotides 12380-13493 of SEQ ID NO: 4. Therefore, it does not appear that SEQ ID NO: 4 represents GenBank accession number NM_005577.1.

Appropriate correction is required.

Claim Objections

Claim 50 is objected to because of the following informalities: Claim 50 recites SEQ ID NO: 95 twice. Appropriate correction is required.

Claims 52 and 53 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 50 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 50 is directed to the antisense compound of claim 1, where the antisense compound "comprises" a nucleotide sequence selected from the group "consisting" of SEQ ID NOs: 85-93 and 95. Since the antisense compound can comprise additional elements, the antisense compound cannot be selected from the group consisting of, or closed to, specific sequences.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Cai et al. (WO 2004/108916 A1).

The instant claims are directed to an antisense compound 15 to 30 nucleobases in length targeted to apolipoprotein(a), wherein said compound is at least 90% complementary to nucleotides 12380-13493 of instant SEQ ID NO: 4, wherein the compound is an oligonucleotide and is single-stranded.

Cai et al. teach an antisense oligonucleotide that is a single stranded primer that is 96% complementary to nucleotides 12805-12829 of instant SEQ ID NO: 4 (see nucleotides 2-26 of SEQ ID NO: 6 of Cai et al.- SCORE result #58 in search titled "20070502_094837_us-10-559-647-4_copy_12380_13493.sl.rge"). Since the oligonucleotide of Cai et al. meets the structural limitations of the instant claims, the antisense compound necessarily meets the instant limitation of being "targeted to a nucleic acid molecule encoding apolipoprotein(a)", as instantly claimed.

Therefore, the instant invention is anticipated by Cai et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 6, 8-11, 17, 54-60 and 62-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruoy et al. (WO 99/35241), in view of Morishita et al. (Circulation, 1998, 98, pages 1898-1904) and Baracchini et al. (U.S. patent 5,801,154).

The instant claims are directed to an antisense compound 15 to 30 nucleobases in length targeted to apolipoprotein(a), wherein said compound is at least 90% complementary to nucleotides 12380-13493 of instant SEQ ID NO: 4, wherein the compound is an oligonucleotide and is single-stranded. The oligonucleotide is further

specified to be a chimeric antisense oligonucleotide or to have specific chemical modifications.

Ruoy et al. teach antisense nucleic acids that are capable of specifically hybridizing with a nucleic acid encoding apolipoprotein(a) and down regulating gene expression (see page 23, first full paragraph). Ruoy et al. teach that preferably the antisense sequence is at least 20 nucleobases in length and that the antisense oligonucleotides can be modified to improve their stability and selectivity.

Ruoy et al. do not teach antisense oligonucleotides that are at least 90% complementary to the coding region (nucleotides 12380-13493) of apolipoprotein(a) SEQ ID NO: 4 or the specific modifications that are instantly claimed.

Morishita et al. disclose three phosphorothioate modified ribozyme oligonucleotides and one DNA based oligonucleotide targeted to kringle 4 of apolipoprotein(a) (see page 1899, methods and figure 1A). Morishita et al. also disclose that the expression of ribozyme oligonucleotides targeting human apolipoprotein(a) inhibited human apolipoprotein(a) protein expression in HepG2 cells (see figures 2A and 2B), but not plasminogen concentrations (see figure 3A). The ribozymes taught by Morishita et al. are targeted to the coding region (see Figure 1A and results, paragraph 1), which demonstrates that it was known in the art at the time the invention was made to target the coding region of apolipoprotein(a).

Baracchini et al. teach antisense oligonucleotides with modifications such as phosphorothioates, 2'-O-methoxyethyl sugar moieties, and 5-methylcytosine nucleobase modifications (columns 6 and 7). Additionally, Baracchini et al. teach

chimeric oligonucleotides containing two or more chemically distinct regions (column 8). Baracchini et al. teach antisense oligonucleotides that it is preferable to target the coding region and for antisense oligonucleotides to be 8-30 nucleobases in length. Baracchini teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Baracchini et al. teach that it is preferable for antisense oligonucleotides to be 100% complementary to the selected target.

Baracchini et al. teach that typically chimeric oligonucleotides are "gapped" oligonucleotides (or "gapmers") in which a region of deoxynucleotides (the "gap"), preferably containing at least four contiguous deoxynucleotides, is flanked by regions of modified nucleotides, preferably 2'-sugar modified nucleotides. In a preferred embodiment, the flanking regions (or "wings") contain 2'-alkoxy or 2'alkoxyalkoxy modifications, more preferably 2'-methoxyethoxy. In preferred embodiments the backbone may be phosphorothioate throughout or may be phosphodiester in the "wings" and phosphorothioate in the "gap". In other preferred embodiments, chimeric oligonucleotides may be "winged" oligonucleotides (or "wingmers" or hemichimeras) in which there is a deoxy "gap", preferably at least 4 contiguous deoxynucleotides, flanked on either the 5' or the 3' side by a region of modified nucleotides. Again, the flanking region (or "wing") preferably contains 2'-alkoxy or 2'alkoxyalkoxy modifications, more preferably 2'-methoxyethoxy and the backbone may be phosphorothioate throughout or may be phosphodiester in the "wing" and phosphorothioate in the "gap". Other

configurations of chimeric oligonucleotide are also comprehended by this invention. These may involve other modifications of the sugar, base or backbone, preferably in the oligonucleotide wing(s).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to make an antisense oligonucleotide to apolipoprotein(a) as taught by Ruoy et al. with the chemical modifications taught by Baracchini et al. targeted to the coding region, as taught by Morishita et al. and Baracchini et al.

One would have been motivated to target the coding region of apolipoprotein(a) with the antisense oligonucleotides of Ruoy et al. because Morishita et al. teach targeting ribozymes to the coding region of apolipoprotein(a) for inhibition of target gene expression and Baracchini et al. teach that the coding region is a preferable target region for antisense oligonucleotides in general. Due to the size and accessibility of the coding region, there would be a reasonable expectation of success to target an antisense oligonucleotide to this region, as demonstrated by Baracchini et al.

One would have been motivated to incorporate a chimeric configuration, 2'-O-methoxyethyl sugar moieties, phosphorothioate linkages, or 5-methylcytosine modifications into the antisense oligonucleotides of Ruoy et al. because Baracchini et al. teaches each of these elements and teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases.

One would have a reasonable expectation of success for each of the instant modifications to benefit the antisense oligonucleotides of Ruoy et al. because the chemistry was well known, as demonstrated by Baracchini et al. and Morishita et al. Ruoy et al. teaches that it is beneficial to modify antisense oligonucleotides, whereas Baracchini et al. and Morishita et al. teach specific chemical modifications for the same benefits.

Therefore, the invention of the above claims would have been obvious, as a whole, at the time the instant invention was made.

Claims 1, 3, 6, 8-11, 17, and 54-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruoy et al. (WO 99/35241), in view of Morishita et al. (Circulation, 1998, 98, pages 1898-1904) and Baracchini et al. (U.S. patent 5,801,154), as explained in the 35 U.S.C. 103(a) rejection above, further in view of Ramasamy (US 6,525,191 B1).

The instant claims are directed to an antisense compound 15 to 30 nucleobases in length targeted to apolipoprotein(a), wherein said compound is at least 90% complementary to nucleotides 12380-13493 of instant SEQ ID NO: 4, wherein the compound is an oligonucleotide and is single-stranded. The oligonucleotide is further specified to be a chimeric antisense oligonucleotide or to have specific chemical modifications.

Ruoy et al., Morishita et al., and Baracchini et al. do not teach bicyclic nucleic acid sugar moieties.

Ramasamy teaches bicyclic nucleic acid sugar moieties for antisense oligonucleotides and teaches that such moieties may have superior inhibitory properties.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to incorporate a bicyclic sugar moiety into the chimeric antisense oligonucleotide with a gapmer configuration targeted to the coding region of apolipoprotein(a), as explained above.

One would have been motivated to incorporate a bicyclic sugar moiety as taught by Ramasamy because Baracchini et al. teaches that other configurations of chimeric oligonucleotide are also comprehended which may involve other modifications of the sugar, base or backbone, preferably in the oligonucleotide wing(s) and Ramasamy teaches that bicyclic sugar moieties may have superior inhibitory properties.

One would have a reasonable expectation of success to incorporate a bicyclic sugar moiety into the antisense oligonucleotides discussed above because Ramasamy teaches that such modifications may have superior inhibitory properties in oligonucleotides and Baracchini et al. teaches the incorporation of various chemical modifications to enhance the activity of antisense oligonucleotides.

Therefore, the invention of the above claims would have been obvious, as a whole, at the time the instant invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 6, 8-11, and 54-57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, and 4-11 of copending application 10/485,113. Although the conflicting claims are not identical, they are not patentably distinct from each other because they contain compounds that are overlapping in scope. The instant application and application '113 have the same inventors.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Application '113 recites a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human apolipoprotein (a), wherein said compound specifically hybridizes with a nucleic acid molecule encoding human apolipoprotein(a) and inhibits the expression of human apolipoprotein(a). Application '113 teaches that

the coding region is a region that can be targeted effectively. Claim 11 is specifies that the compound specifically hybridizes with an active site. Application '113 teaches the compound to be an antisense oligonucleotide, wherein the compound can comprise a modified internucleoside linkage, more specifically a phosphorothioate linkage; a modified sugar moiety, more specifically a 2'-O-methoxyethyl sugar moiety; a modified nucleobase, more specifically a 5-methylcytosine modified nucleobase; or the oligonucleotide is a chimeric oligonucleotide (see claims 2 and 4-10). The compounds of application '113 and the instant compounds are obvious over each other.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amy H Bowman
Examiner
Art Unit 1635

JON E. ANGELL, PH.D.
PRIMARY EXAMINER

AHB